

Applicants: William C. Olson and Paul J. Maddon  
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**REMARKS**

Claims 87-88, 91-95, 98-100 and 102-109 are pending in the subject application. By this Amendment, applicants have canceled the pending claims without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims in this or another application. Applicants have also added new claims 110-137.

New claims 110-137 are fully supported in the specification as follows. Claims 110 and 112: page 22, lines 5-10 and line 33 to page 23, line 7; page 17, lines 20-24; page 13, lines 28-29 and line 34 to page 14, line 8, as amended in the October 4, 2004 Amendment; page 14, lines 26-30; page 18, line 35 to page 19, line 2; page 19, lines 10-13; page 31, lines 10-18; Claims 111 and 113: page 17, lines 27-29; page 31, lines 17-18; Claims 114 and 115: page 22, lines 35-36; Claims 116, 120, 127 and 133: page 23, lines 3-4; page 19, lines 2-4; Claims 117, 121, 128 and 134: page 23, lines 5-7; page 19, lines 4-6; Claims 118, 122, 129 and 135: page 19, lines 30-34; Claims 119 and 130: page 18, line 37 to page 19, line 2; page 22, line 37 to page 23, line 1; Claims 123 and 136: page 18, lines 35-36; page 22, lines 36-37; Claims 124 and 137: page 23, line 2 1-2; Claims 125, 126, 131 and 132: page 22, lines 33-35; page 13, lines 28-29 and line 34 to page 14, line 8, as amended in the October 4, 2004 Amendment. Thus, applicants maintain that the addition of these new claims does not raise any issue of new matter. Accordingly, applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 110-137 will be pending and under examination.

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### **The Invention**

The claimed invention provides an isolated nucleic acid encoding a polypeptide comprising a heavy chain of an anti-CCR5 antibody or a portion thereof containing three CDR regions. The invention also provides an isolated nucleic acid encoding a polypeptide comprising a light chain of an anti-CCR5 antibody or a portion thereof containing three CDR regions. The three CDR regions of each polypeptide comprise consecutive amino acids, the sequences of which are identical to the sequences of CDR regions present in a heavy and a light chain, respectively, of monoclonal antibody PA14, PA8, PA9, PA10, PA11 or PA 12. Further, each encoded polypeptide, in combination with a second polypeptide, binds to an epitope of CCR5 comprising amino acid residues in (1) the N-terminus (Nt) of CCR5, (2) one of the three extracellular loop (ECL) regions of CCR5, or (3) a combination of the Nt or ECL regions of CCR5.

In a preferred embodiment of this invention, the sequences of the three CDR regions are identical to the sequences of CDR regions present in monoclonal antibody PA14.

### **Allowable Subject Matter**

Applicants acknowledge the Examiner's statement that claims 91-92, 98, 102, 105-106 and 108 contain allowable subject matter, i.e., nucleic acids that encode a polypeptide that corresponds to at least six CDR regions of an antibody or a polypeptide that binds to an epitope of CCR5, wherein the epitope comprises amino acid residues in (1) an N-terminus of CCR5, (2) one of the three extracellular loop regions of CCR5,

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or (3) a combination thereof.

In response, applicants maintain that based on the arguments and remarks set forth below, new claims 110-137 are in condition for allowance.

**Rejections under 35 U.S.C. §112, first paragraph**

The Examiner rejected claims 87-88, 93-95, 99-100, 103-104 and 107-108 under 35 U.S.C. §112, first paragraph, since the specification allegedly enables isolated nucleic acid molecules that encode a minimum of 6 CDR regions of the deposited antibodies. The Examiner stated that, additionally, claims 87-88, 93-95, 99-100, 103-104 and 107-108 would be deemed allowable if applicants amend the claims to recite a specific binding activity, such as incorporating the limitations recited in claim 91 into the rejected claims.

The Examiner noted applicants' assertion that the claimed invention is fully enabled by the specification as filed, and reviewed applicants' arguments in support of this assertion. The Examiner also stated that applicants' submission has been considered but, however, is not found persuasive. According to the Examiner, the issue at hand is that an artisan skilled in the art would not be able use the full scope of the claimed invention without an undue burden of experimentation. The Examiner also stated that applicants have not taught the skilled artisan how to use polypeptides that correspond to one CDR region or portions thereof of an antibody.

The Examiner asserted that the skilled artisan would not be able to use the full scope of the claimed invention without an

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undue burden of experimentation, as demonstrated by Williams et al. (1989) Proc. Natl. Acad. Sci. U.S.A. 86: 5537-5541, and Williams et al. (1991) J. Biol. Chem. 266: 5182-5190 (collectively "Williams"). The Examiner stated that applicants have cited these two references to demonstrate that the claimed invention is enabling for the nucleic acid molecules that encode peptides that correspond to a minimum of one CDR region of an antibody. The Examiner also stated that while applicants are correct to note that Williams teaches of peptides that corresponds to a CDR region of an antibody, applicants have, however, neglected to note that Williams teaches that a peptide that is directed to a CDR region of a light chain does not exhibit the same activity as that of its corresponding full antibody. In this regard, the Examiner noted that the peptide does not inhibit DNA replication whereas its corresponding full antibody inhibits DNA replication. The Examiner also noted that it is only after modification is made to the peptide sequence that Williams was able to demonstrate that the peptide exhibits biological activity.

The Examiner stated that Williams also notes, in other studies, that a peptide that corresponds to the heavy chain variable region fails to exhibit biological activity similar to that of its corresponding antibody. The Examiner also stated that William does not teach the skilled artisan how to use peptides based on antibody CDR region structures. The Examiner further stated that Williams only teaches how to make these peptides, wherein only modified versions of these peptides exhibit similar biological activity as that of its corresponding antibody. The Examiner additionally stated that Williams et al. does not demonstrate that the peptides,

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modified or non-modified, have the same biological activity as its corresponding antibody would command.

The Examiner also stated that Bourgeois et al. (1998) J. Virol. 72: 807-810 ("Bourgeois") teaches the same as Williams. The Examiner noted that Bourgeois is a reference cited by applicants to demonstrate the peptides corresponding to a CDR region can bind to a target antigen and exhibit biological activity of the intact antibody. The Examiner further stated that Bourgeois teaches that of the six CDRs, only one CDR has neutralizing activity that is similar to that of its corresponding antibody.

The Examiner acknowledged that applicants are correct to note that in some species, functional single-domain antibodies naturally lack light chains and contain only three CDR loops contributed by the heavy chain. However, the Examiner stated that this occurrence is not applicable and relevant to the claimed invention. The Examiner noted that the polypeptides of antibodies encoded by the claimed nucleic acids occur within conventional antibody molecules, specifically murine antibodies and not camelid antibodies. The Examiner stated that murine antibodies differ from camelid antibodies structurally in that murine antibodies naturally consist of two light chains and two heavy chains, and consist of three CDRs for each chain whereas camelid antibodies are functional single-domain antibodies that naturally lack light chains and contain only three CDR loops.

The Examiner stated that, in the present case, contrary to the teachings of Taub et al. (1989) J. Biol. Chem. 264: 259-265 ("Taub"), and Bourgeois, applicants have failed to teach the

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skilled artisan how to use the full scope of the claimed invention without an undue burden of experimentation. The Examiner also stated that the difference between the instantly claimed antibody polypeptides and polypeptides disclosed in the cited references is that Taub and Bourgeois teach the skilled artisan how to use their specific peptides without an undue burden of experimentation. The Examiner further stated that in both instances, Taub and Bourgeois are specific to a particular CDR region that each recognizes as important to the biological activity that they chose to observe. The Examiner also stated that in the present case, applicants provide no such correlative analysis. The Examiner additionally stated that, if anything, the teachings of Taub and Bourgeois only further exemplify the amount of experimentation that the skilled artisan must conduct to practice the full scope of the claimed invention.

The Examiner agreed with applicants that even in an antibody consisting of heavy and light chains and comprising six CDRs, not all these CDRs necessarily bind to the target antigen. The Examiner also stated that all six CDRs must, however, be present to maintain the antigen binding specificity and affinity. The Examiner further stated that, in the instant case, Davies et al. (1996) Proc. Natl. Acad. Sci. U.S.A. 93: 7-12 ("Davies"), a reference cited by applicants to demonstrate that not all six CDRs necessarily bind to the target antigen, recognizes the importance of all six CDRs. The Examiner noted that Davies experimented with the Fab portion of an antibody, which comprises a light chain and heavy chain, each of which contains three CDRs, thus totaling six CDRs.

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The Examiner stated that, lastly, it appears that applicants have taken the teaching of Rudikoff et al. (1982) Proc. Natl. Acad. Sci. U.S.A. 79: 1979) ("Rudikoff") and the Examiner's summation of Rudikoff's teaching out of its intended context. The Examiner stated that, in the instant case, she relies on the teaching of Rudikoff to demonstrate that the level of unpredictability in the antibody art is extremely high, while pointing to Rudikoff for support. The Examiner further stated that Rudikoff teaches that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function. The Examiner also stated that applicants further affirm this level of unpredictability with their presentation of teachings by Parhami-Seren et al. (2001) J. Immunol. 167: 5129-5135 ("Parhami-Seren"). The Examiner additionally stated that Parhami-Seren teaches that two mutations in a CDR region of an antibody resulted in significant loss of binding.

The Examiner stated that in the instant case, applicants have not taught the skilled artisan how to use polypeptides that are encoded by the claimed nucleic acid molecules corresponding to less than six CDR regions of an antibody. The Examiner also stated that, currently, the pending claims are directed to a multitude of polypeptides that the skilled artisan would not know how to use without an undue burden of experimentation. The Examiner reminded applicants that the above lack of enablement analysis is based on the culmination of the factors set forth in the previous Office Action, Wands factors, in view of the discussion above and the level of unpredictability that is associated with the instant antibody art. The Examiner concluded that the claimed invention

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remains rejected for not being enabling for its full scope.

In response, applicants respectfully traverse the above "enablement" rejections. Nevertheless, without conceding the correctness of the Examiner's position, applicants note that the pending claims have been canceled, and that new claims 110-137 presented herein are directed to subject matter which the Examiner has stated is allowable. Applicants note that the subject matter of the canceled claims is represented in new claims 110-137. Accordingly, applicants hereinbelow respond to the instant rejections as if they referred to new claims 110-137.

Applicants refer to the Examiner's statement on page 2, item 4, of the Office Action that the specification enables isolated nucleic acid molecules that encode a minimum of six CDR regions of the deposited antibodies. In response, applicants note that, except in the case of single chain antibodies (such as are specified in new claims 124 and 137), a polypeptide constituent of an antibody encoded by a single nucleic acid would not comprise six CDR regions of the antibody. Instead, the nucleic acid would normally encode a polypeptide comprising one or more CDR regions of a heavy chain, or a polypeptide comprising one or more CDR regions of a light chain. The combination of two heavy and light chain polypeptides, together comprising six CDR regions, may then form an antigen binding site which binds specifically to a particular antigen.

Applicants note that new independent claim 110 provides an isolated nucleic acid encoding a polypeptide comprising a heavy chain of an anti-CCR5 antibody or a portion thereof



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containing three CDR regions, wherein the three CDR regions comprise consecutive amino acids identical in sequence to the sequences of CDR regions present in a heavy chain of monoclonal antibody PA14, PA8, PA9, PA10, PA11 or PA12, and wherein the polypeptide in combination with a second polypeptide binds to an epitope of CCR5.

New claim 112, the only other independent claim, provides an isolated nucleic acid encoding a polypeptide comprising a light chain of an anti-CCR5 antibody or a portion thereof containing three CDR regions, wherein the three CDR regions comprise consecutive amino acids identical in sequence to the sequences of CDR regions present in a light chain of monoclonal antibody PA14, PA8, PA9, PA10, PA11 or PA12, and wherein the polypeptide in combination with a second polypeptide binds to an epitope of CCR5. Applicants note that the isolated nucleic acids claimed in claims 110 and 112 collectively encode six CDR regions of an anti-CCR5 antibody (brought together by the combination of the encoded polypeptides), which the Examiner has stated is allowable.

The Examiner also stated on page 2, item 4, of the Office Action that the rejected claims would be deemed allowable if they were amended to recite a specific binding activity, such as incorporating the limitations recited in claim 91 into the rejected claims. In response, applicants note that new claims 110 and 112, the only independent claims, recite the specific binding activity previously recited in now canceled claim 91. That is, the combination of the polypeptides encoded by the nucleic acids of claims 110 and 112 bind to an epitope of CCR5 comprising amino acid residues in (1) an N-terminus of CCR5, (2) one of three extracellular loop regions of CCR5, or (3) a

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combination of (1) and (2). Thus, applicants maintain that claims 110 and 112 are directed to subject matter which the Examiner stated in the Office Action is allowable. Further, applicants maintain that, based on the specification as filed, one skilled in the art would be able to make the claimed invention without undue experimentation.

Applicants note that claims 111 and 113-137 depend, directly or indirectly, from claims 110 or 112 and therefore necessarily possess all the elements of claims 110 or 112. Applicants submit, therefore, that the remarks made above regarding claims 110 and 112 also obviate the grounds of rejection of claims 111 and 113-137 under 35 U.S.C. §112, first paragraph. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the grounds of the "enablement" rejection of claims 88, 93-95, 99-100, 103-104 and 107-108.

### **Conclusion**

Applicants note that the new claims presented herein are directed to subject matter which the Examiner has stated is allowable. In view of the foregoing remarks, applicants therefore respectfully request that the Examiner reconsider and withdraw the grounds of the "enablement" rejections set forth in the January 13, 2005 Final Office Action, and earnestly solicit allowance of new claims 110-137 now pending in the subject application.

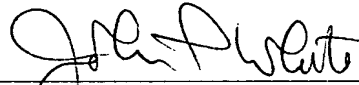
If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at

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the number provided below.

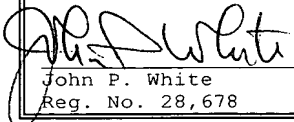
A fee of sixty dollars is required for a one-month extension of time for responding to the January 13, 2005 Final Office Action. A fee of three hundred and eighty dollars (\$380.00) is also deemed necessary in connection with the filing of additional claims and multiple dependent claims in this Amendment. Accordingly, a check in the total amount of FOUR HUNDRED AND FORTY DOLLARS (\$440.00) is enclosed. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White  
Registration No. 28,678  
Attorney for Applicants  
Cooper & Dunham, LLP  
1185 Avenue of the Americas  
New York, New York 10036  
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:  
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